New insights into the surgical treatment of mitral regurgitation

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Discussion and Future Perspectives

The mitral valve and mitral valve repair techniques have been subject of extensive research over the past few decades. Mitral valve repair techniques have evolved considerably and have become the gold standard for common conditions such as degenerative mitral regurgitation (MR). In less common conditions, such as ischemic mitral regurgitation (IMR) (chronic and acute), MR caused by (special forms of) endocarditis or MR in heart transplant recipients, repair techniques are still subject of much debate. Although it has become clear from different studies that mitral valve repair is generally superior to valve replacement in terms of preservation of left ventricular (LV) function, survival rates, reoperation rates, endocarditis risk, thrombo-embolic complication rates, the need for lifelong anticoagulant drugs, and costs [1-4], it is not always clear whether valve repair is indeed better or even feasible for specific, less common forms of MR. This thesis provides new insights into the surgical treatment of these specific and often complex forms of MR.

Chronic ischemic mitral regurgitation (CIMR) occurs in approximately 20-25% of patients followed up after myocardial infarction (MI) and in 50% of those with post-MI congestive heart failure (CHF) and its incidence is likely to increase in the next few decades as the population ages and as survival rates for acute MI continue to improve [5-10]. The presence of CIMR adversely affects prognosis, increasing mortality and the risk of CHF in a graded fashion according to CIMR severity [6,10]. Although mitral valve repair with undersized ring annuloplasty (usually combined with concomitant coronary artery bypass grafting (CABG)) has become the preferred treatment strategy [11-13], the overall CIMR persistence and recurrence rate (moderate or severe CIMR) remains high (up to 30% after 6 months and up to 60% after 3-5 years) [14,15] and after a 10-year follow-up there does not appear to be a survival benefit of a combined procedure compared to CABG alone (10-year survival rate for both is approximately 50%) [16,17]. Undersized ring annuloplasty treats annular dilatation, but does little to reduce annular flattening and it does not address the main pathophysiological mechanism of CIMR, which is ischemia-induced LV remodeling with papillary muscle displacement and apical leaflet tethering [18]. In fact, undersized ring annuloplasty may potentiate leaflet tethering by increasing posterior leaflet tethering [19]. Annular dilatation and flattening and leaflet tethering and flattening reduce leaflet coaptation and increase leaflet and chordal strain [18,20]. Strain is the main cause of limited repair durability and CIMR recurrence after repair, which may explain the difficulty in demonstrating a survival benefit of annuloplasty for CIMR [16,17,19,20]. Patients with advanced mitral valve tethering who are at risk of annuloplasty failure based on preoperative three-dimensional (3D) and two-dimensional (2D) echocardiographic parameters (such as a P3 tethering angle ≥29.9° or a tenting area ≥2.5 cm^2, a tenting height ≥10 mm, a posterior tethering angle ≥45°, an anterior tethering angle ≥39.5°, an interpapillary muscle distance >20 mm, a LV end-systolic volume ≥145 ml, a systolic sphericity index >0.7) may benefit from mitral valve replacement with preservation of the subvalvular apparatus or from annuloplasty combined with new repair techniques targeting the subvalvular apparatus including the LV [18,21]. These new mechanism-based repair techniques were designed to improve repair durability and include second-order chordal cutting, papillary muscle repositioning by a variety of techniques and ventricular approaches using external ventricular restraint devices or the Coapsys device [18]. Although promising, at this point these new procedures still lack investigation in large patient cohorts with long-term follow-up. They will, however, be the subject of much anticipated and necessary ongoing and future research.

In order to reduce the high CIMR persistence and recurrence rate after repair with undersized annuloplasty rings, new annular and valvular procedures were introduced in addition to the new subvalvular and ventricular procedures mentioned in the previous paragraph [22,23]. CIMR repair with posterior leaflet augmentation (with bovine pericardium) combined with ring annuloplasty or CIMR repair with a saddle-shaped annuloplasty ring are promising, reproducible techniques that can reduce tethering and increase leaflet coaptation and repair durability, but they remain annular/valvular solutions to a subvalvular problem, which render them susceptible to CIMR recurrence [18,22,23]. The ultimate objective will be to tailor the ideal combination of annular, valvular, chordal, papillary muscle and ventricular repair techniques based on preoperative clinical and echocardiographic characteristics to achieve the best result in each individual patient with CIMR. In conjunction with advancements made in 3D echocardiographic mitral valve imaging this should lead to a “continuum of surgical techniques” for CIMR that can be customized to the individual patient’s needs.

The pathophysiological mechanisms of CIMR have gradually been unravelled in the past decades. The main cause of CIMR is ischemia-induced LV remodeling with papillary muscle displacement and apical tethering (and flattening) of the mitral valve leaflets combined with annular dilatation (and flattening) [18]. The role of papillary muscle infarction (PMI) in the development op CIMR is still debated. Our late gadolinium-enhanced cardiac magnetic resonance imaging study has shown that CIMR rates are higher in patients with PMI four months after primary percutaneous coronary intervention for ST-elevation MI, but PMI is not an independent predictor of CIMR [24]. Instead, independent predictors of CIMR include age, infarct size, tethering height, and interpapillary muscle distance [24].

Acute ischemic mitral regurgitation (AIMR) caused by post-myocardial infarction papillary muscle rupture (post-MI PMR) is a rare, but life-threatening condition that requires immediate surgical intervention [25-29]. Post-MI PMR usually involves the posteromedian papillary muscle due to its single blood supply [29-32]. Partial or incomplete post-MI PMR is generally a good indication for repair (with established repair techniques such as tri- or quadrangular resection combined with ring annuloplasty or height- and length-adjusted papillary muscle reimplantation) and provides good short- and long-term results [31]. PMR type and adjacent tissue quality determine the feasibility and durability of repair [31]. Complete post-MI PMR generally requires mitral valve replacement [32,33]. Due to high risks (intraoperative mortality of 4.2% and in-hospital mortality of 25.0%) some surgeons may be reluctant to operate certain patients with post-MI PMR [32]. In order to improve surgical decision making and to improve the quality of informed consent we sought to identify which patients were at highest risk by identifying independent predictors of in-hospital mortality. A logistic EuroSCORE ≥40%, an EuroSCORE II ≥25%, complete PMR, and intraoperative intra-aortic balloon pump requirement independently predict in-hospital mortality [32]. Overall long-term survival is 49.5±7.6% after 10 years and based on the results from our cohort there is no difference in overall long-term survival between repair and replacement and between patients who did and did not undergo concomitant CABG [33]. Logistic EuroSCORE ≥40%, EuroSCORE II ≥25%, preoperative inotropic drug support and mitral valve replacement without preservation of the subvalvular apparatus are independent predictors of a lower overall long-term survival [33]. Whenever possible, the subvalvular apparatus (i.e. the papillary muscle-annular continuity) should be preserved in these patients to improve long-term survival.

In even less common forms of MR such as Libman-Sacks endocarditis or severe MR in heart transplant recipients repair is feasible and durable with established mitral valve repair techniques (such as tri- or quadrangular resection combined with ring annuloplasty, neochords combined with ring annuloplasty, or isolated ring annuloplasty) [34,35].

This thesis provides new insights into the surgical treatment of more complex forms of MR. Important developments in 3D diagnostic imaging modalities and surgical techniques for these complex forms of MR may also have implications for more common and less complex forms of MR.

The future of mitral valve surgery is expected to show an increasing shift towards minimally invasive (robotic) and percutaneous approaches and custom-made repair techniques and annuloplasty rings based on advanced 3D mitral valve imaging [36].

In the past decades we have begun to unravel the delicate anatomy of the mitral valve and the elegant way in which the anatomy of the interrelated parts of mitral valve reduce strain and stress on itself during the cardiac cycle. Maintaining or restoring the delicate geometric and functional integrity of the mitral valve is essential to durable mitral valve surgery. This principle is not only important in mitral valve repair, but also in mitral valve replacement (i.e. maintaining the subvalvular apparatus).

In more complex mitral valve disease such as CIMR different mechanisms go on to produce MR to different extents and the relative contributions of these mechanisms may change over time, partially due to the delicate interrelated geometry of the mitral valve [18]. In order to achieve durable mitral valve repair it is essential to determine what the relative contributions of those mechanisms are and the effects they have on annular, leaflet, chordal, and papillary muscle strain. Advanced computer models based on 3D echocardiographic data will allow us to construct a 3D image of the regurgitant mitral valve during a full cardiac cycle and it will allow us to test what the effect of different repair techniques are on mitral regurgitation and annular, leaflet, chordal, and papillary muscle strain. At this point time-consuming manual segmentation of 3D echocardiographic images is required to generate a 3D mitral valve rendering (Fig. 1A,B). Therefore, work is in progress to develop automated segmentation techniques that will allow image processing and segmentation in minutes rather than hours (Fig. 1C) [37]. These mathematical computer models will pave the way for custom-made mitral valve repair tailored to a patient's individual needs. Such a tailored approach based on predictive mathematical models is to be expected within the next decade, because 3D imaging and predictive mathematical models are currently evolving at a rapid pace. Real time 3D echocardiography and strain analysis (Fig. 1D) will also become an important part of intraoperative assessment of repair results. Advancements in 3D printing will even allow us to print 3D models of the regurgitant mitral valve at any point during the cardiac cycle (Fig. 1E) [38]. Further advancements in 3D printing may even allow production of custom-made annuloplasty rings and mitral valve prostheses.

Ultimately superior predictive computer models would not only include anatomical and strain related aspects, but also clinical patient-related factors (such as age, comorbidity and LV function) and procedure-related factors (such as risk of repair failure with prolonged cardiopulmonary bypass and aortic cross-clamping) in order to decide between a sophisticated costum-made repair or mitral valve replacement with preservation of the subvalvular apparatus. There is an ongoing debate in the literature regarding the advantages of repair versus replacement in patients with CIMR. Indeed, a recent randomized study among 251 patients with severe CIMR showed no significant difference in LV reverse remodeling, major adverse cardiac or cerebrovascular events, functional status, quality of life, or survival 12 months after repair or chordal-sparing mitral valve replacement [39]. Moderate or severe MR recurrence was significantly higher after repair (32.6% vs. 2.3%, $P < 0.001$) and patients with recurrence showed no reverse remodeling,

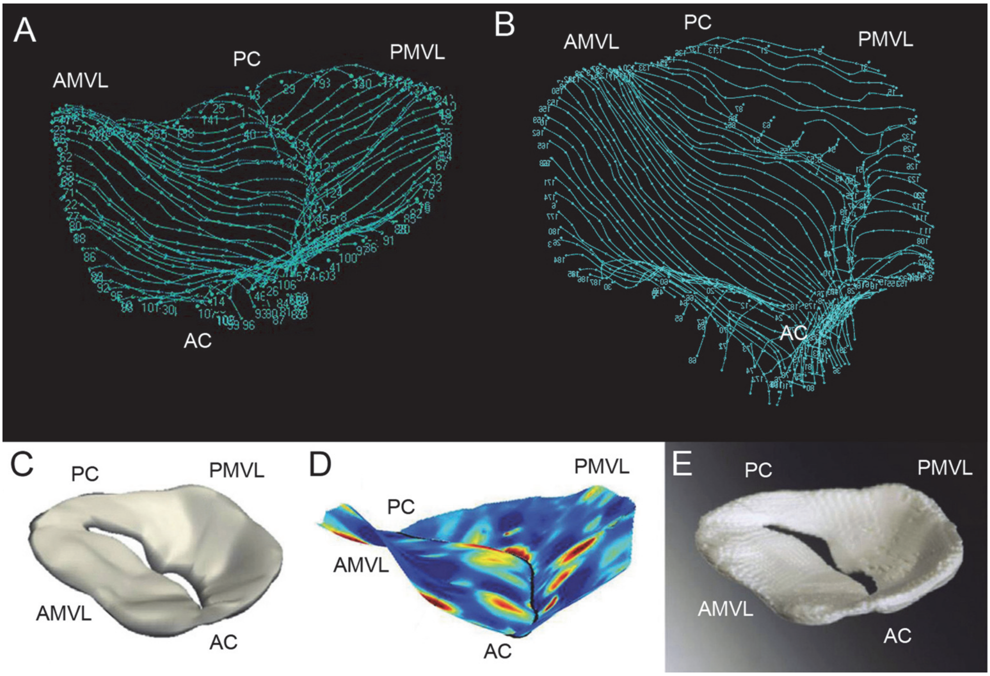

Figure 1. Advanced 3D mitral valve imaging models

(A) Oblique view of a 3D rendering of a normal mitral valve after manual image segmentation; (B) oblique view of a 3D rendering of a severely tethered mitral valve (CIMR) after manual image segmentation (notice annular dilatation and flattening and leaflet tethering with loss of leaflet curvature and leaflet coaptation); (C) Oblique view of a 3D rendering of a tethered mitral valve (CIMR) after automated image segmentation; (D) Oblique view of a 3D rendering of a normal mitral valve with leaflet curvature assessment (the pseudocolor map in the figure depicts regional Gaussian curvature in the anterior and posterior mitral leaflets; deeper blue colors represent more negative Gaussian curvature, which is indicative of a hyperbolic (saddle-shaped) curvature and reduced leaflet strain/stress); (E) Oblique view of a physical printed 3D mitral valve model based on C.

A-E provided by: the Gorman cardiovascular research group.

AC = anterior commissure; AMVL = anterior mitral valve leaflet; PC = posterior commissure; PMVL = posterior mitral valve leaflet.

indicating advanced stages of tethering [39]. The results need to be interpreted carefully, because the study has several important drawbacks. No data was provided regarding tethering severity or the types of repair used and as a consequence no attempt was made to identify patient subgroups that might benefit from repair. Disadvantages of mitral valve replacement may still make it worthwhile to attempt repair, especially because newer percutaneous mitral valve replacement techniques [40-42] such as "the valve in ring concept" may be used as bail-out procedures for recurrent MR after repair and lower the threshold for repair in these more complex forms of MR [43].

To conclude, sophisticated 3D imaging modalities and computer models combined with sophisticated new, tailor-made repair techniques, annuloplasty rings and mitral valve prostheses are expected to truly revolutionize mitral valve surgery in the next decade.

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